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Claims

1. A method of embolus therapy comprising administering into the vasculature (including the capillaries) of a perfused zone of tissue in a human or non-human animal subject a composition comprising particles of a size or formulation selected to generate emboli at a target site within said subject, characterised in that said composition further comprises an iodinated contrast agent, MR active agent or ultrasound contrast agent imageable marker to identify the extent of embolization, and that as said particles are used solid water-insoluble particles 1-50 micrometers in size of a non-radioactive diagnostically effective compound in a non-polymeric particulate matrix selected from the group consisting of insoluble metal oxides, insoluble metal salts, inert metals, glass, ceramic particles and porous particles or vesicles encapsulating a non-radioactive diagnostically effective compound or a solution thereof, and in that embolus location is detected by a diagnostic imaging technique.

2. A method as claimed in ~~claim~~ 1, wherein said particles are 5-25 micrometers in size.

3. A method as claimed in claim 1, wherein said particles are 10-20 micrometers in size.

4. A method as claimed in ~~claim~~ 1, wherein vascular collateralization of the embolized vascular bed is absent or sufficiently delayed such that said reduced perfusion is therapeutically effective.

5. A method as claimed in ~~any of the preceding claims~~ claim 1, wherein said water-insoluble particles comprise an insoluble phosphate salt of the formula

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$M_{10}(PO_4)_6A_z$.

wherein

M = Ba, Ca, Cd, Mg, Pb or Sr
A = OH^-, Cl^-, F^- or CO_2^{-2}
Z = 2 if A is univalent, 1 if A is divalent.

6. A method as claimed in ~~claim 5~~, wherein said insoluble phosphate salt is hyroxyapatite, $Ca_{10}(PO_4)_6OH_2$.

7. A method as claimed in ~~any of the preceding claims~~, wherein said composition further comprises a conventional contrast agent.

8. A method of radiation therapy of a tissue comprising the steps of:

i) administering into the vasculature including the capillaries of a perfused zone of tissue in a human or non-human animal subject a composition comprising particles of a size or formulation selected to generate emboli at a target site within said subject, characterised in that as said particles are used solid water-insoluble particles 1-50 micrometers in size of a non-radioactive diagnostically effective compound in a non-polymeric particulate matrix selected from the group consisting of insoluble metal oxides, insoluble metal salts, inert metals, glass, ceramic particles and porous particles or vesicles encapsulating a non-radioactive diagnostically effective compound or a solution thereof; and

ii) applying a therapeutic dose of radiation, wherein said particles act as a radiation therapy sensitizer.

9. A method as claimed in claim 8, wherein said composition further comprises a conventional contrast agent.

10. A method as claimed in claim ~~9~~ 8, wherein said conventional contrast agent acts as a radiation therapy sensitizer.

11. A method as claimed in ~~any one of claims 8 to 10~~ claim 8, wherein said therapeutic dose of radiation originates from a source external to said tissue.

12. A method as claimed in ~~any one of claims 8 to 10~~ claim 1, wherein said therapeutic dose of radiation originates from a source internal to said tissue.

13. A method as claimed in claim ~~12~~ 8, wherein said internal source of radiation comprises implanted ^{125}I.

14. A method as claimed in claim ~~9~~ 8, wherein said conventional contrast agent is a radio-dense material.

15. A method as claimed in claim ~~14~~ 8, wherein said radio-dense material comprises an iodinated contrast agent.

16. A method as claimed in claim ~~15~~ 8, wherein said iodinated contrast agent is selected from the group consisting of 6-(ethoxycarbonyl)hexyl bis(3,5-acetylamino)-2,4,6-triiodobenzoate (NC67722), (ethoxycarbonyl)methyl bis(3,5-acetylamino)-2,4,6-triiodobenzoate (NC12901), 1-(ethoxycarbonyl)pentyl bis(3,5-acetylamino)-2,4,6-triiodobenzoate (NC70146) and

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ethyl bis(3,5-acetylamino)-2,4,6-triiodobenzoate (NC8883).

17. A method as claimed in claim ~~9~~ 8, wherein said conventional contrast agent is both an MR active and X-ray absorbing material.

18. A method as claimed in claim ~~17~~ 8, wherein said conventional contrast agent is selected from the group consisting of gadolinium oxide, gadolinium oxalate and manganese-doped hydroxyapatite.

19. A method of chemoembolic therapy comprising administering into the vasculature of a perfused zone of tissue in a human or non-human animal subject particles of a size or formulation selected to generate emboli at a target site within said subject, in combination with a therapeutic agent, characterised in that as said particles are used solid water-insoluble particles of a non-radioactive diagnostically effective compound or vesicles encapsulating a non-radioactive diagnostically effective compound or a solution thereof, and wherein said therapeutic agent is a promoter of vascular growth.

20. A method of chemoembolic therapy comprising administering into the vasculature including the capillaries of a perfused zone of tissue in a human or non-human animal subject particles of a size or formulation selected to generate emboli at a target site within said subject, in combination with a therapeutic agent, characterised in that as said particles are used solid water-insoluble particles 1-50 micrometers in size of a non-radioactive diagnostically effective compound in a non-polymeric particulate matrix selected from the group consisting of insoluble metal oxides, insoluble metal salts, inert metals, glass, ceramic particles and porous particles or vesicles encapsulating a non-

radioactive diagnostically effective compound or a solution thereof, and wherein said therapeutic agent is an inhibitor of vascular growth.

21. A method as claimed in claim 19, wherein said promoter of vascular growth is selected from the list comprising vascular endothelial growth factor (VEGF), vascular endothelial growth factor-related protein, basic fibroblast growth factors (bFGF and FGF-3), epidermal growth factor, hepatocyte growth factor, insulin-like growth factor, placental growth factor, placental proliferin-related protein, platelet-derived growth factor, platelet-derived endothelial growth factor, proliferin, proliferin-related protein, transforming growth factors α and β and tumor growth factor α.

22. A method as claimed in claim 20, wherein said inhibitor of vascular growth is selected from the list comprising tecogalan sodium (Daiichi), AGM-1470 (Takeda/Abbott), CM101 (Carbomed), mitaflaxone (Lipha), GM-1603 (Glycomed), rPF4 (Repligen), MPF-4 (Lilly), recombinant angiostatin (Entremed), endostatin, thalidomide (Entremed), DC101 (ImClone Systems), OLX-514 (Aronex), raloxifene hydrochloride (Lilly), suramin sodium (Parke-Davis), IL-12 (Roche), marimastat (British Biotech), and CAI (NCI).

23. A method as claimed in ~~either one of claims 19 and 20~~ claim 19, wherein said therapeutic agent is a cytotoxin.

24. A method as claimed in claim ~~23~~ 19, wherein said cytotoxin is selected from the group comprising carboplatin, mitoxantrone, epirubicin, mitomycin C, decarbazine, vinblastine, cisplastin, interferon, dactinomycin, hydroxyurea, carmustine, methyl CNNU, interleukin-2, cyclophosphamide, amsacrine and

doxorubicin.

25. A method as claimed in ~~either one of claims 19 and 20~~ claim 19, wherein said therapeutic agent is a biotherapeutic agent.

26. A method as claimed in claim ~~25~~ 19, wherein said biotherapeutic agent is selected from the group consisting of antisense nucleic acids, diphtheria toxin and ricin A chain.

27. A method as claimed in ~~either one of claims 19 and 20~~ claim 19, wherein said therapeutic agent is a nuclear agent.

28. A method as claimed in ~~either one of claims 19 and 20~~ claim 19, wherein said particles are administered prior to administration of said therapeutic agent.

29. A method as claimed in ~~either one of claims 19 and 20~~ claim 19, wherein said particles are administered after administration of said therapeutic agent.

30. A method as claimed in ~~either one of claims 19 and 20~~ claim 19, wherein said particles are coadministered with said therapeutic agent.

31. A method as claimed in ~~any of claims 28 to 30~~ claim 19, wherein said generated emboli are temporary and said therapeutic agent is targeted.

32. A method as claimed in ~~any of claims 28 to 30~~ claim 19, wherein said generated emboli are temporary and said therapeutic agent comprises genetic material.

33. A method as claimed in ~~either one of claims 19 and 20~~ claim 19, wherein said therapeutic agent is a material that enhances another therapeutic intervention.

34. A method as claimed in claim ~~33~~ 19, wherein said therapeutic intervention is hyperthermia or photolytic therapy.

35. A method of identifying local pharmacokinetics in tissue comprising administering into the vasculature including the capillaries of a perfused zone of tissue in a human or non-human animal subject particles of a size or formulation selected to generate emboli at a target site within said subject optionally in combination with an imageable agent, characterised in that as said particles are used solid water-insoluble particles 1-50 micrometers in size of a non-radioactive diagnostically effective compound in a non-polymeric particulate matrix selected from the group consisting of insoluble metal oxides, insoluble metal salts, inert metals, glass, ceramic particles and porous particles or vesicles encapsulating a non-radioactive diagnostically effective compound or a solution thereof.

36. Use of solid water-insoluble particles of a non-radioactive diagnostically effective compound or vesicles encapsulating a non-radioactive diagnostically effective compound or a solution thereof as defined in ~~any one of claims 1 to 35~~ claim 1 for the manufacture of an embolus generating pharmaceutical composition for use in embolus therapy.

37. A pharmaceutical composition comprising embolus forming contrast-effective particles together with a physiologically tolerable sterile liquid carrier medium, characterised in that as said particles are used solid water-insoluble particles of a non-radioactive diagnostically effective compound or vesicles encapsulating a non-radioactive diagnostically effective compound or a solution thereof, as defined in ~~any one of claims 1 to 35~~ claim 1.

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